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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,257	01/30/2006	Herbert Schwarz	HABERMANN-1	5164

23599 7590 06/27/2008

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EXAMINER	
YAO, LEI	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
06/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,257	SCHWARZ ET AL.	
	Examiner	Art Unit	
	LEI YAO	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *5,6,13-21,24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/16/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *PTOL90*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 1 (claims 1-12 and 22-25) with species B cell lymphoma and antibody BBK-2 in the reply filed on 4/28/2008 is acknowledged.

The traversal is on the ground(s) that the Office has not established an undue search burden to examine the full scope of present claims. This is not found persuasive because the elected invention of treating tumor expressing CD137 and non-elected invention of treating undesired or overactive immune response are two distinct methods which involve different method steps and modes of operations. Two inventions require different patient populations or biological samples used in the method. Searching the method of inhibiting of undesired immune response and the method of treating tumor would not be co-extensive and would impose a burden for the examination. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Regarding the species election, after reviewing the elected species in light of the prior art, the species fibrosarcoma is joined to the species lymphoma for examination at this time.

Claims 1-26 are pending.

Claims 13-21 and 26 as being drawn to a nonelected inventions and claims 5, 6, 24 and 25 as being drawn to a nonelected species are withdrawn from further consideration pursuant to 37 CFR 1.142(b), there being no allowable generic or linking claim.

Claims 1-4, 7-12, and 22-23, drawn to a method of treating tumor comprising CD137 expressing tumor to the extent of B cell lymphoma and fibrosarcoma and antibody BBK-2, are examined on the merits.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 6/16/2005 are/is partially considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed, wherein the item 3-6 of page 1 in the IDS fails to comply with the provisions of 37 CFR 1.97-1.98 and MPEP 609 because the

inventor's names are missing in the items. It has been placed in the application file, but the information referred to herein has not been considered as to the merits.

Sequence Requirements

A first office action can be performed on this application, however, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Although the claims in the instant application are not drawn to specific sequences, the disclosure contains sequences that need SEQ ID numbers for figure 8-A and 8-B. If these sequences are found in the sequence listing filed 6/16/2005, Applicants need only insert the appropriate SEQ ID Nos. However, if these sequences are not part of the listing, then Applicants need to comply with the sequence rules. Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance.

Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply (see attached form, PTO L90).

Claim Objections

Claims 3 and 22 are objected to because of the following informalities: the claim reciting "the amino acid sequence of human CD137 shown in fig 8B that lists the amino acid sequence of CD137. Amending the claims by adding the SEQ ID NO of CD137 would be appreciated.

Claim Rejections - 35 USC § 101 and 112 2nd Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

MPEP 2173.05(q) "Use" Claims:

> Attempts to claim a process without setting forth any steps involved in the process generally raises an issue of indefiniteness under 35 U.S.C. 112, second paragraph. For example, a claim which read: "A process for using monoclonal antibodies of claim 4 to isolate and purify human fibroblast interferon." Was held to be indefinite because it merely recites a use without any active, positive steps delimiting how this use is actually practiced. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Other decisions suggest that a more appropriate basis for this type of rejection is 35 U.S.C. 101. In *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967), the Board held the following claim to be an improper definition of a process: "The use of a high carbon austenitic iron alloy having a proportion of free carbon as a vehicle brake part subject to stress by sliding friction." In *Clinical Products Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966), the district court held the following claim was definite, but that it was not a proper process claim under 35 U.S.C. 101: "The use of a sustained release therapeutic agent in the body of ephedrine absorbed upon polystyrene sulfonic acid." Although a claim should be interpreted in light of the specification disclosure, it is generally considered improper to read limitations contained in the specification into the claims. See *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969) and *In re Winkhaus*, 527 F.2d 637, 188 USPQ 129 (CCPA 1975), which discuss the premise that one cannot rely on the specification to impart limitations to the claim that are not recited in the claim.

Claims 1-4, 7, and 8 are rejected under 35 U.S.C. § 101 because the claims recite "use of a CD137 antagonist for the preparation of a medicament for the treatment of CD137-expressing tumor", which are not presented in the format of a proper process claim according to MPEP 2173.05(q) above.

The following is a quotation of the **second paragraph** of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7, and 8 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "use of a CD137 antagonist for the preparation a medicament for the treatment of CD137-expressing tumor", it merely recites a use without any active, positive steps delimiting how this use is actually practiced. It is not clear that the method is drawn to using a CD137 antagonist for preparing a medicament for treating a CD137 expressing tumor OR using a CD137 antagonist for treating a tumor.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-4, 7, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by B. Kwon (US Patent No. 6303121, issued Oct 2001) as evidenced by sequence search result.

The claims recite use of a CD137 antagonist for the preparation of a medicament for the treatment of CD137-expressing tumor, where CD137 antagonist is antibody to CD137 BBK-2, wherein the tumor are B-cell lymphoma, or/and chronic lymphocytic leukemia.

Due to the indefiniteness of the term "use of a CD137 antagonist" as stated above, the Office, for the art purpose, interprets the claims as preparation of medicament (pharmaceutical composition) comprising CD137 antagonist antibody for treating CD137 expressing tumors (elected antibody).

For this rejection the intended use of the medicament for treatment of CD137 expressing tumor is given no patentable weight.

It is noted that alternative name of CD137 is 4-1BB or H4-1BB.

Kwon discloses antagonist CD137 (H4-1BB) antibody, BBK-2, and a pharmaceutical composition comprising the antibody for treating a disease comprising treating tumor (col 5, line 54+, col 23, line 56+ abstract, last line). The amino acid sequence of CD137 is identical to the human CD137 in figure 8B (SEQ ID NO: 2, search result attached).

2. Claims 9-10, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Aruffo et al., (US Patent 6210669, issued April 2001).

The claims are interpreted as a method of treating a tumor patient comprising administering an effective amount of CD137 antibody, wherein the antibody is directed to at least one epitope of the amino acids of human CD137.

It is noted that alternative name of CD137 is 4-1BB.

Aruffo et al., disclose a method of treating a cancer with an antibody to CD137 (4-1BB) comprising the step of administering the antibody to an individual with a tumor comprising P815 mastocytoma and AG104 spontaneous sarcoma. Aruffo et al., first disclose monoclonal antibodies to 4-1BB and a method of enhancing lymphocyte killing and cytotoxicity to tumor cells in a host comprising administering the host an effective dose of an anti-4-1BB antibody (col 1-2 and bridging col 8-9). Aruffo

et al., then disclose that the tumor is suppressed in the mice receiving the antibody (figure 8) and also disclose that the treated mice survive longer than the mice without treatment (figure 9).

The prior art disclosed CD137 antibody appears to meet the requirements of the instant claimed method of treating tumor patient. Regarding the limitations of CD137 antagonist antibody, Aruffo et al., do not specifically teach that the antibody used in the method is an antagonist antibody to CD137 and the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Claims 9-11, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al., (Cancer Research, vol 61, page 2031-2037, 2001).

The claims are set forth above, wherein the tumor is fibrosarcoma (claims 11).

Kim et al., disclose a method of treating a tumor comprising fibrosarcoma with a monoclonal antibody to CD137 (4-1BB), 1D8, or 3E1, comprising the step of administering the antibody to an individual (mice) with a tumor. Kim et al disclose the treatment with antibody result in significant prolongation of survival of the mice with i.c. tumor (page 2032, col 1, para 1, page 2033, figure 3 and abstract, line10+).

The prior art disclosed CD137 antibody appears to meet the requirements of the instant claimed method of treating tumor patient. Regarding the limitations of CD137 antagonist antibody, Kim et al., do not specifically teach that the antibody used in the method is an antagonist antibody to CD137 and the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish

patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquires set forth in Graham V. john Deere Co., 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 25 U.S. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or obviousness

1. Claims 9, 11, and 12 are also rejected under 35 U.S.C. 103(a) as being unpatentable Aruffo et al., (US Patent 6210669, issued April 2001) or Kim et al., (Cancer Research, vol 169, page 1792-1800, Aug. 2002).

The claim 9 is set forth above, wherein the tumor is B-cell lymphoma (claim 11), wherein the B-cell lymphoma is chronic lymphocytic leukemia (CLL, claim 12).

The teachings of Aruffo et al., and Kim et al., are set forth above.

Aruffo et al., specifically teach the method of enhancing lymphocyte, proliferation, activation and cytotoxicity to tumor cells (col 1-2 and bridging col 8-9)

Kim et al., also teach enhancing lymphocyte, proliferation, activation and cytotoxicity to tumor cells (abstract and page 2036 col 2 last paragraph) and teach the antibody used for treating variety of tumors comprising sarcoma, melanoma, carcinoma etc. (page 2031, col 2)

Although Aruffo et al., and Kim et al., do not specifically teach the tumor cells are B-cell lymphoma or CLL. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the methods to treat all tumors comprising B cell lymphoma and CLL with expected result. One of ordinary skill in the art at the time the invention was made would have been motivated to use the teachings of the references in order to benefit for treating any cancer comprising B cell lymphoma and CLL by increasing the immune response by stimulating cytotoxic function of T cells because Aruffo et al., and/or Kim et al., suggest to use antibody to CD137 (4-1BB) for immunotherapy for cancer by increase the cytotoxic T activity to tumor cells. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to treat cancer comprising B cell lymphoma and CLL because Aruffo et al., and Kim et al., have already shown the antibody to CD137 could be used for treating variety of tumors comprising sarcoma, melanoma, carcinoma etc. by reducing the tumor size and prolong the life of the mice. Therefore, the references in combination teach every limitation of the claims and the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

The prior art disclosed CD137 antibody appears to meet the requirements of the instant claimed method of treating tumor patient. Regarding the limitations of CD137 antagonist antibody, Aruffo et al., or Kim et al., do not specifically teach that the antibody used in the method is an antagonist antibody to CD137 and the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Claims 1-4, 7-12, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwon B. (US Patent 6303121 issued Oct. 2001) in view of Broll et al., (Am J Clin Pathol, Col 115 page, 543-549, 2001) or Schwarz et al (Blood, vol 85, page 1043-1052, 1995).

The claims are set forth above, wherein the antibody to CD137 is antagonist antibody BBK-2.

Kwon B. teaches antagonist antibody to CD137 (4-1BB), BBK-2 (col 5, line 54+, col 23, line 56+) and suggest to use the antibody to treat cancer or tumor (abstract, last line).

Kwon B. does not specifically teach treating B-cell lymphoma comprising chromic lymphocytic leukemia (CLL).

Broll et al., teach CD137 (ILA/4-1BB) expressed in activated hematopoietic cells (page 543, col 2, para 1).

Schwarz et al., teach ILA/4-1BB expressed in B-cell lymphoma cells, for example Raji cell (figure 6, page 1048).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the antibody BBK-2 in the methods to treat a tumor comprising B-cell lymphoma and/or CLL with expected result. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of the references in order to benefit for treating CD137 expressing tumor comprising B-cell lymphoma abd/or CLL because Kwon suggests using antibody to treat tumors (abstract). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teachings to treat a cancer comprising B-cell lymphoma and/or CLL because both Broll et al., and Shcwarz et al., have already shown those cells expressing CD137 (ILA/4-1BB) protein and Kwon et al., teach the antibody and use the antibody for treating tumors. Therefore, the references in combination as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643